

AHRQ Systematic Review Surveillance Report

CER #134: Pharmacotherapy for Adults with Alcohol-Use Disorders in Outpatient Settings, May 2014

Surveillance Report: September 2017

Summary of Key Findings:

- Key Question 1: Which medications improve **consumption** outcomes for adults with AUDs in outpatient settings?
 - Original conclusions are likely current for efficacy and comparative effectiveness of medications approved for use (disulfiram, acamprosate, and naltrexone).
 - New evidence of efficacy for off-label medications suggests these conclusions may not be current. We identified 16 new studies. These provided additional evidence for baclofen (4) topiramate (3), citalopram (1) and nalmefene (1); and new evidence about four medications not included in the original review (7). Results for topiramate and nalmefene were consistent with previous review, but those for baclofen and citalopram were not.
- Key Question 2: Which medications improve **health outcomes** for adults with AUDs in outpatient settings?
 - Original conclusions are likely current for efficacy and comparative effectiveness.
- Key Question 3: What **adverse effects** are associated with medications for adults with AUDs in outpatient settings?
 - Original conclusions are likely current for harms and comparative harms of medications approved for use
 - New evidence about baclofen harms suggests these conclusions may not be current. We identified 6 new studies (4 RCTs and 2 observational), with inconsistent results. For other off-label medications (nalmefene, topiramate, quetiapine) conclusions are likely current.
- Key Question 4: Are medications for treating adults with AUDs effective **in primary care settings**?
 - Original conclusions are likely current. We identified one small study using gabapentin (off-label) in primary care.
 - Two large studies (STEP and CHOICE) are underway and may have data in the next two years.
- Key Question 5: Are any of the medications more or less effective than other medications for **sub-groups**: men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?
 - Original conclusions are likely current.
 - Several small studies provide new evidence in subgroups (ie, those who are non-obese, smokers, HIV-infected, cocaine dependent; those with anxiety, depression, Hepatitis C, bipolar disorders) with a variety of on- and off- label meds. However, these are unlikely to change report conclusions.
- Key Question 6: Are any of the medications more or less effective for adults with **specific genotypes** (e.g., mu-opioid receptor gene [OPRM1])?
 - Original conclusions (insufficient evidence) may not be current. We identified six new studies for disulfiram (2), acamprosate (1), naltrexone (1), and topiramate (2). However, sample sizes were fairly small, a variety of genotypes were reported, and results were inconsistent.

Overall Assessment of Currency:

While some new evidence is available, conclusions of the original review are likely current

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Conflict of Interest:

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

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Introduction

The purpose of the surveillance process for the Agency for Healthcare Research and Quality's (AHRQ) Evidence-based Practice Center (EPC) Program is to determine whether the conclusions of a systematic review (SR) are current. The surveillance process examines the conclusions to the key questions as written, and does not evaluate the currency of the original scope (i.e., key questions, included interventions).

Comparative Effectiveness Review (CER) #134 titled “**Pharmacotherapy for Adults with Alcohol-Use Disorders (AUD) in Outpatients Settings**” was originally released in May 2014.¹ Since then, it has been cited 64 times by PubMed articles, and downloaded 2,360 times.

The **Key Questions** (KQ) are:

Key Question 1a: Which medications are **efficacious** for improving **consumption outcomes** for adults with AUDs in outpatient settings?

Key Question 1b: How do medications for adults with AUDs **compare** for improving **consumption outcomes** in outpatient settings?

Key Question 2a: Which medications are **efficacious** for improving **health outcomes** for adults with AUDs in outpatient settings?

Key Question 2b: How do medications for adults with AUDs **compare** for improving **health outcomes** in outpatient settings?

Key Question 3a: What **adverse effects** are associated with medications for adults with AUDs in outpatient settings?

Key Question 3b: How do medications for adults with AUDs **compare** for **adverse effects** in outpatient settings?

Key Question 4: Are medications for treating adults with AUDs effective in **primary care settings**?

Key Question 5: Are any of the medications more or less effective than other medications for men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?

Key Question 6: Are any of the medications more or less effective for adults with specific **genotypes** (e.g., related to polymorphisms of the mu-opioid receptor gene [OPRM1])?

Methods

Our surveillance assessment began in January 2017. Briefly, we searched for literature published since the last search date in the original SR. Then, we asked content experts involved in the original SR for their input. We compiled these opinions, discussed as a group, and determined our conclusions.

Literature Searches

The literature search was updated twice for this brief. For the initial search, consistent with the AHRQ Methods Guide,² an information specialist (RR) reviewed the original search strategy and conducted a series of highly precise searches in PubMed. RR limited the searches to those studies published since the last search date in the original SR (December 2013) through January 1, 2017. RR also searched for current and ongoing research on websites of relevant associations, foundations and societies, including the National Institute on Alcohol Abuse and Alcoholism. Additionally, RR searched ClinicalTrials.gov for recently completed trials.

We updated the search through July 30, 2017 using two methods, a citation search and related article search. (Details are in Methods, Appendix A) For the citation search, a clinical researcher (JH) modified the method of Janssens et al.³ Based on the literature, JH selected a purposive sample⁴ of key articles from the original SR to detect any signals, that is, new data that would change the results. The purposive sample yielded 17 key articles, 10% of the 167 included in the original SR. JH used the Scopus database to search for new publications (January to July 2017) that had cited any of the key articles. JH downloaded all results, deleted duplicates and selected those published after January 1, 2017.

For the related article search the clinical researcher (JH) used the Simplified Search Strategy method described by Rice et al,⁵ using key articles from the SR. JH used the 'related articles' feature in PubMed for each key article, and selected those published between January and July 2017.

Study Selection

Using the same inclusion and exclusion criteria as the original systematic review (see Appendix B), one investigator (KW) reviewed the titles and abstracts of the search results. We included systematic reviews and meta-analyses, whether or not they were included (as a study design) in the original systematic review. For systematic reviews and meta-analyses, we considered findings only if all included studies met inclusion criteria. . Reviews for which one or more study did not meet our criteria were used to identify potentially relevant primary research.

For the updated search, the clinical researcher (JH) reviewed titles, abstracts and full reports for the citation and related-articles searches. JH used the same inclusion and exclusion criteria as the original systematic review (see Appendix B) described above. Because of the newer methods, JH erred on the side of over-inclusion.

Expert Opinion

We developed a findings matrix by summarizing new evidence alongside the original SR key questions and conclusions. We sent the findings matrix to subject matter experts. (Appendix C) We requested their comments on whether the SR conclusions were current and if we had missed any relevant new studies.

FDA Black Box Warnings

We searched the FDA Medwatch online database website for black box warnings for all drugs mentioned in the systematic review.

Compilation of Findings and Assessment of Currency

To assess whether individual SR conclusions were current, we constructed a summary table (Appendix D) that compared the key questions and conclusions from the original SR, findings of the new literature searches, and the expert opinion. We qualitatively compared original SR conclusions with the new input from the literature and experts, and categorized whether each conclusion was current as follows:

New Evidence	Responding Experts	Assessment of Original Conclusion
None, or supports the original finding	Concur	Likely current
Some new or conflicting evidence	Disagree	May not be current
Major change in evidence (groundbreaking study, FDA warning)	Concur	Out of date

To assess whether the entire systematic review was current, we considered the strength of the original conclusion, and how new evidence contributed to the number of studies, number of participants, and consistency of results. We weighted conclusions for the FDA-approved medications more heavily than evidence for off-label medications, as these were the main points of the original review. Further, we prioritized results for KQ1, KQ2, and KQ3, because the original review found insufficient evidence for all comparisons and outcomes for KQ4, KQ5, and KQ6.

Results

Literature Search

A total of 43 of articles were examined for potential to change the results of the original systematic review. 41 came from the literature search, and 2 came from expert reviewers.

The initial search (December 2013-January 2017) identified 95 unique titles. Upon abstract review, 71 studies were excluded because they did not meet the original systematic review inclusion criteria. The remaining 24 studies were examined as new evidence.⁶⁻²⁹

The Scopus citation approach for the updated search (January 2017-July 2017) yielded 61 unique citations after January 1, 2017. Of these, 54 were excluded at title or abstract review, and three at full review. Four remaining studies met inclusion criteria and were included as new evidence.³⁰⁻³³

The PubMed related article approach for the updated search identified 113 unique citations after January 1, 2017. Of these, 92 were excluded at title/abstract review, and five at full review. Three were already identified in the Scopus search,³⁰⁻³² thus 13 remaining studies were included as new evidence.³⁴⁻⁴⁶

Experts contributed two citations^{47,48}

Of the 43 of articles examined for potential to change the results of the original systematic review, the number that pertained to each key question was unevenly distributed. There were

22 for KQ1, three for KQ2, 15 for KQ3, one for KQ4, 20 for KQ5, and six for KQ6. For background, we also included a recent meta-analysis of disulfiram efficacy that we found in the PubMed related articles search⁴⁹ and preliminary descriptions of two new trials on AUD treatment in primary care: STEP⁵⁰ and CHOICE trials.⁵¹ Finally, we note that the Cochrane Collaboration has published a protocol for a systematic review of baclofen efficacy.⁵² Detailed findings from these studies are found in Appendix C.

FDA Black Box Warnings

We found no FDA black box warnings

Expert Opinion

We contacted eight subject matter experts (two original authors and six technical expert panel (TEP) members) for their opinions and recommendations. Two experts responded with a completed matrix; one provided comments by email.

All reviewers concurred that overall, the systematic review did not need updating, or that updating was premature. One commented that AHRQ might consider a smaller update for newer/off-label medications. He noted that evidence on baclofen, in particular, is accumulating rapidly.

Compilation of Findings

Appendix D shows the original key questions, the conclusions of the original systematic review with strength of evidence (SOE), the results of the literature search, expert opinion, and the assessment of the currency of the systematic review. Details of each study are in this appendix.

- Key Question 1: Which medications improve **consumption** outcomes for adults with AUDs in outpatient settings?
 - 1a: Efficacy conclusions are likely current for medications approved for use. We found one study each on disulfiram (n=109)²⁹, acamprosate (n=327)¹³ which supported the SR conclusions and were too small to likely change the SOE. A single small trial of a lower dose of naltrexone (n=128)²⁴ with conflicting results is unlikely to change prior conclusions that were based on >10 trials with >2000 participants in the systematic review.
 - The original SR reviewed the efficacy of off-label use of baclofen, topiramate, citalopram, nalmefene, varenicline, aripiprazole, atomoxetine, desipramine, fluvoxamine, imipramine, olanzapine, ondansetron, paroxetine, and fluoxetine. We identified 16 new studies since 2013. These included articles about for baclofen (4) topiramate (3), citalopram (1), nalmefene (1) and varenicline (2); and about four medications not included in the original review (5).
 - Baclofen conclusions may not be current. Prior conclusions (insufficient SOE) were based on 2 trials (164 participants). We identified three new RCTs with 440 participants, but efficacy results are inconsistent.^{23,26,43} A Cochrane review is planned.⁵²
 - Topiramate conclusions are likely current. We identified two RCTs and one meta-analysis.^{8,15,20} Although the single studies conflict and vary by which drinking outcome was measured, the meta-analysis supports prior conclusions.

- Citalopram conclusions may not be current. The one new study (n=265) greatly increases the number of patients studied, and results (placebo better than treatment) conflict with prior evidence.¹⁰
- Nalmefene conclusions may not be current. One study (n=422) showed a decrease in number of heavy drinking days, consistent with prior evidence.²⁸
- Varenicline conclusions are likely current. Two new studies (n=40²⁵ and n=160¹¹) found no effect, and are small studies that are unlikely to change the current conclusion.
- In the original SR, insufficient evidence was found for the efficacy of aripiprazole, atomoxetine, desipramine, fluvoxamine, imipramine, olanzapine, ondansetron, paroxetine, fluoxetine and valproic acid. We found no new studies in this update.
- We found new efficacy studies for four other off-label medications (zonisamide, levetiracetam, mecamlamine and gabapentin). These were not in the scope of original SR and are included for information only.
- 1b: Comparative effectiveness: conclusions for acamprosate vs naltrexone are likely current. One new study (n=225) found no significant difference between acamprosate and naltrexone on number of drinking days, or return to any drinking.¹⁸ However this same study suggests that disulfiram is superior to acamprosate and naltrexone, which is not consistent with the original review. There is no new evidence for off-label medications.
- Key Question 2: Which medications improve **health outcomes** for adults with AUDs in outpatient settings?
 - 2a: Efficacy: Original conclusions are likely current. SOE was insufficient for approved medications disulfiram, acamprosate, naltrexone, and no new studies were identified. Two new studies [one each for topiramate (n=106)²⁰ and baclofen (n=64)²⁶] are too small to change prior conclusions
 - 2b: Comparative effectiveness: Original conclusions (insufficient SOE) are likely current. One study (n=243) compared disulfiram vs acamprosate vs naltrexone.¹⁸ Depression decreased and all patients showed significant improvement in sleeping, action, pain, and mood dimensions, with no difference between medications. This single study is unlikely to change prior conclusions
- Key Question 3: What **adverse effects** are associated with medications for adults with AUDs in outpatient settings?
 - 3a: Harms: original conclusions are likely current for medications approved for use. The original body of literature was large and SOE was moderate for harms of acamprosate and naltrexone. We found one study for naltrexone (n=128)²⁴, and no new studies for acamprosate which reported harms. The SOE for harms of disulfiram was not graded in the original report. We found only one report listing harms of disulfiram (n=29)²⁷.
 - Harms: original conclusions are likely current for off-label medications, except for baclofen.
 - The harms of baclofen may not be current. The original SR did not report on harms of baclofen. We identified six new publications, four RCTs^{22,23,31,43} and two large observational studies^{33,35} The most serious side effects were reports of increased anxiety and intentional overdose among baclofen users.

- Conclusions are likely current for nalmefene. New evidence (one study, n=422)²⁸ supports prior conclusions of increased side effects compared to placebo (moderate SOE).
 - Conclusions are likely current for topiramate. Two studies (n=30 and n=85) are consistent with prior conclusions of increased cognitive dysfunction compared to placebo^{7,15} (moderate SOE).
 - Conclusions are likely current for quetiapine. In the prior SR, no studies reported harms. We found one study (n=90) that reported weight gain as the only side effect⁹.
 - 3b: Comparative harms: original conclusions are likely current. No new studies were identified for any comparisons.
- Key Question 4: Are medications for treating adults with AUDs effective in **primary care settings**?
 - Original conclusions are likely current. The only new evidence is a small study using gabapentin in primary care.²¹ Two large studies are underway (STEP and CHOICE) and may have data in the next few years^{51,52}.
 - Key Question 5: Are any of the medications more or less effective than other medications for **sub-groups**: men or women, older adults, young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders?
 - Original conclusions are likely current. SOE for this KQ was not done. We identified 20 studies which provide new evidence in subgroups (ie, those who are non-obese, smokers, HIV-infected, cocaine dependent; those with anxiety, depression, Hepatitis C, bipolar disorders) with a variety of on- and off label meds. Most studies were small, and results were inconsistent. However, a systematic review of naltrexone in women (7 studies, n=903) suggested that naltrexone may lead to modest decreases in quantity of drinks and time to relapse in women.³⁷
 - Key Question 6: Are any of the medications more or less effective for adults with **specific genotypes** (e.g., mu-opioid receptor gene [OPRM1])?
 - Original conclusions might be current (insufficient SOE). We identified six new studies that assessed genotypes and response to medication: disulfiram (two studies), acamprosate (one study), naltrexone (one study), and topiramate (two studies). These new studies might change conclusions, but our content experts did not concur.

We identified no new large ground-breaking studies or FDA boxed warnings since the original systematic review was published.

Overall Assessment of Currency

New evidence examined in this surveillance assessment suggests that the original review is likely current. For three approved medications, there is very little new data on efficacy or comparative effectiveness for alcohol consumption, health outcomes, or harms. Thus the major conclusions for KQ1 (alcohol consumption), KQ2 (health outcomes), and KQ3 (harms) are likely current. Similarly, conclusions for the efficacy of six of the eight off-label medications that were originally included are unlikely to change with the limited new data that has been published, with two exceptions. For citalopram, a single large RCT reports that treatment worsened drinking outcomes compared with placebo. Evidence for baclofen now includes five studies (over 600

patients) with mixed results for efficacy, and five studies (three RCTs, two observational studies) for harms. The reports of intentional overdose with baclofen are concerning. The Cochrane group plans a systematic review of the safety and efficacy of baclofen for alcohol use disorders. New information for KQ4, KQ5 and KQ6 is limited by the small number of studies, and heterogeneity of comparisons and outcomes. Thus, overall, we conclude that the original systematic review is likely current.

Appendix A: Methods

Appendix A: Methods

The “Pharmacotherapy for Alcohol Use Disorders” systematic review (AUD report) was published in May 2014, and its most recent search was October 2013. The SRC followed the usual search strategy for the December 2013 to January 2017 timeframe. Because of constrained resources, responsibility for this surveillance project was transferred from the EHC Program Scientific Resource Center to AHRQ. This transition resulted in a 6-month time lag. The need for an updated search provided an opportunity to try alternative search strategies.

We found two recent articles that described alternative search strategies for full systematic reviews, and adapted them to fit the needs of a surveillance / update report. Rice et al described a simplified search strategy using OVID or Pubmed.⁵ (<https://www.ncbi.nlm.nih.gov/pubmed>). The authors noted *“In contrast to OVID, the PubMed “similar articles” search works in advance of indexing, may be more useful for rapid/short interval reviews.”* Therefore, we used their PubMed approach. First, choose several key articles from the original review (e.g., the three largest and three most recent studies). If the review includes multiple articles from the same study, choose the main article in the search. Second, using the PubMed identifier (PMID), find each article in PubMed and click on the “similar articles” feature. Third, limit the results to the pertinent search dates and save results to the PubMed clipboard. After searching for each key article, download/export the clipboard for review.

Our second approach was adapted from that of Janssens et al.⁵³ Choose key articles from the original review (e.g., the two largest studies). Enter the PMID for each article into Web of Science (Scopus) (<https://www.scopus.com/home.uri>) and search forward to detect new citations, excluding book citations. After searching for each key article, export the results for review. Create a database of all results. Delete duplicates, and limit the results to pertinent search dates.

Both methods described selecting two-six key articles from the original review. However, the AUD report included six key questions and more than ten medications. Therefore, we adapted these approaches for the breadth of the AHRQ report. I designed a purposive sample⁴ of citations to detect any signals, that is, new data that would change the results of the existing SR. To do this, I searched the full AUD report and identified all articles published in 2013 as my “recent” sample. Additionally, I identified the largest two articles for two FDA-cleared drugs (acamprosate and naltrexone), and for the named studies (COMBINE, PREDICT, SENSE). To assure that I did not miss a signal from newer or off-label drugs, I identified the largest study for each off-label drug. If studies were the same size, I chose the most recent. If a single study had more than one publication, I included those with different outcomes (ie, health outcomes or genetics or drinking days). I included the single study (a prospective cohort, high risk of bias) that was cited for harms. Of 167 citations (135 studies) in full AUD report, I selected 17 (10%) to inform this update. (Purposive Citations, Appendix Table 1) For studies that could not be initially located because of misspellings or missing information, I used strategies to locate them, such as searching by the second author.

Appendix A: Methods

The limitation of this approach is that I did not confirm my purposive sample with anyone else. However, content experts only identified two additional citations that were missed by the traditional and newer approaches.

Appendix A: Methods

Table 1: Purposive Citations- Key Articles selected to inform update, and number of articles retrieved for each method

First Author	Publication Year	Drug	RoB ¹	Size (n)	Primary reason to include:	Secondary reason to include:	Articles retrieved ² (N)	
							Scopus	PubMed
Kranzler ⁵⁴	2013	naltrexone	Medium	150	Most recent	Genetic	26	143
Berger ⁵⁵	2013	acamprosate	Medium	100	Most recent	Primary care	14	232
Mann ⁵⁶	2013	nalmefene	Medium	600	Most recent	Named study- ESENSE	173	196
Gual ⁵⁷	2013	nalmefene	Medium	710	Most recent		119	176
Mann ⁵⁸	2013	naltrexone, acamprosate	Medium	420	Named study- PREDICT	compares NTX and ACA	62	276
Morgenstern ⁵⁹	2012	naltrexone	Medium	200	Recent	MSM	18	119
Kranzler ⁶⁰	2012	sertraline	Medium	130	Largest for drug		16	97
Anton ⁶¹	2011	naltrexone, acamprosate, gabapentin	Medium	150	Largest for drug	only 3 drug comparison; includes gabapentin	50	135
Garbutt ⁶²	2010	baclofen	Medium	80	Largest for drug		150	271
Stedman ⁶³	2010	quetiapine	High	350	Largest for drug		39	219
Anton ⁶⁴	2008	naltrexone	Medium	600	Largest genetic	Named study-COMBINE	280	199
Narayana ⁶⁵	2008	any	High	75	Harms		0	97
Johnson ⁶⁶	2007	topiramate	Low	160	Largest for drug		352	144
Salloum ⁶⁷	2005	valproic acid	Medium	60	Largest for drug		204	2175
Fawcett ⁶⁸	2000	buspirone	Medium	150	Largest for drug		29	88
Naranjo ⁶⁹	1995	citalopram	High	150	Largest for drug		64	149
Kranzler ⁷⁰	1995	fluoxetine	Medium	138	Largest for drug		241	101
Total retrieved (1995-2017)							1837	4817

¹ RoB: Risk of Bias, as listed in original AUD report

² Initial retrieval before deleting duplicates and limiting dates to January-July, 2017

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

Category	Inclusion	Exclusion
Population	Adults (age 18 years or older) with alcohol-use disorders (as defined in the Introduction). For KQ 5, co-occurring disorders include other mental health or substance use disorders (e.g., depression, cocaine use disorder) and acute or chronic medical conditions (e.g., cirrhosis).	Children and adolescents under 18
Interventions	Medications approved by FDA for treating alcohol dependence (acamprosate, disulfiram, naltrexone) and the following medications, which have been used off-label or are under investigation: amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, gabapentin, imipramine, nalmefene, olanzapine, ondansetron, paroxetine, prazosin, quetiapine, sertraline, topiramate, valproate, varenicline, viloxazine.	Pharmacotherapy for alcohol withdrawal; any drugs not listed; combinations of medications (e.g., studies randomizing subjects to naltrexone plus ondansetron vs. placebo)
Comparators	For KQs 1 through 5, studies must compare one of the medications listed above with placebo or another medication. For KQ 6, studies must compare people who have a specific genotype or allele with people who have different genotypes or alleles.	No comparison; nonconcordant historical controls
Outcomes	Consumption outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days ^a , drinks per drinking day, time to lapse or relapse. Health outcomes: accidents, injuries ^b , quality of life, function, mortality. Adverse effects of intervention(s): withdrawals due to adverse events, nausea/vomiting, diarrhea, anorexia, palpitations, headache, dizziness, cognitive dysfunction, taste abnormalities, paresthesias (numbness, tingling), metabolic acidosis, glaucoma, vision changes, suicidal ideation, insomnia, anxiety, rash.	Craving; cue reactivity
Timing/ Length of follow-up	At least 12 weeks of follow up from the time of medication initiation.	Less than 12 weeks
Settings	Outpatient health care (i.e., non-laboratory) settings, including studies that begin in or recruit subjects from inpatient settings but then follow and assess subjects receiving pharmacotherapy as outpatients. KQ 4 applies to primary care settings only (i.e., internal medicine, family medicine, pediatrics, obstetrics/gynecology, or college and university health clinics).	All other settings; laboratory settings; inpatient settings (if most or all of the study followed inpatients)
Publication Language	English	All other languages
Admissible evidence (study design and other	Original research; eligible study designs include the following: <ul style="list-style-type: none"> For KQs 1, 2, and 4, double-blind RCTs and recent systematic reviews were eligible. 	Case series Case reports Nonsystematic reviews Systematic reviews with searches that ended prior to 2007

Appendix B: Inclusion and Exclusion Criteria from Original Systematic Review

criteria)	<ul style="list-style-type: none"> • For KQ 2b (head-to-head studies reporting health outcomes), prospective cohort studies were also eligible. • For KQ 3 (harms), double-blind RCTs and recent systematic reviews that compare medication with placebo or with another medication were eligible. The following designs were also eligible if they compared 2 or more drugs of interest: nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies. • For KQ 5 (subgroups), double-blind RCTs, recent systematic reviews, nonrandomized controlled trials, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies were eligible, as long as the studies compared 2 or more drugs. • For KQ 6, double-blind RCTs, analyses of subjects from trials, and prospective cohort studies were eligible. 	Systematic reviews that had been updated Editorials Letters to the editor Studies with historical, rather than concurrent, control groups
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FDA=U.S. Food and Drug Administration; KQ=Key Question; RCT=randomized controlled trial.

^a Heavy drinking days were defined as 4 or more drinks per day for women and 5 or more drinks per day for men.

^b Accidents typically refer to motor vehicle accidents. Injuries may be from a wide variety of alcohol-related problems (e.g., violence, falls). We did not use strict definitions for accidents and injuries. Knowing a priori that we would find very little evidence for these outcomes, we used definitions provided by studies and we included studies that did not provide definitions (but that only gave a number of injuries, for example).

Appendix C: Materials sent to expert reviewers

Appendix C: Materials sent to expert reviewers

We sent each reviewer a cover letter and Findings Matrix. Examples are included here.

Example: Cover Letter (email)

Dear XXXX

I have been assigned the task of assessing whether RTI's systematic review "Pharmacotherapy for Alcohol Use Disorders" funded by AHRQ needs an update. The report was released in May 2014. <https://effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productID=1908>

If the findings are no longer current, AHRQ will archive the report. Our surveillance process combines expert assessment with an abbreviated literature search. We have completed the literature search and believe you are in a solid position to know of new findings that might prompt an update. We have two requests:

1. If you are willing to assist us, please complete the attached **Conflict of Interest Disclosure Statement**, and send a pdf of the signed statement to [email]
2. Most importantly, we want your detailed opinion on the principal findings and conclusions for each key question, as taken from the 2014 Executive Summary. We have updated the findings from our targeted literature search in the attached "**Findings Matrix**." For each principal finding, we ask you to consider the following questions:
 - a. Is this conclusion still supported by the evidence?
 - b. Is there other new evidence that may change this conclusion?

You may type your responses directly into and return to me by email. If you would prefer to provide the responses by phone, we can arrange a call. We know that you are extremely busy, but that at the same time, you are aware of the importance of this task. We would appreciate hearing back from you in the next two weeks (by August 11, 2017). If you have any questions about this project, or would like a pdf of any of the new references we found, please feel free to contact me.

Thank you, in advance, for your help.

Appendix C: Materials sent to expert reviewers

Example: Findings Matrix:

Findings Matrix for “Pharmacotherapy for Alcohol Use Disorders”

The first column contains the original findings/conclusion from the Executive Summary of the original Systematic Review “Pharmacotherapy for Alcohol Use Disorders” published in May 2014. Each row refers to a separate conclusion/finding from the full report. In the second column, we summarized results of our recent targeted literature search.

Please **add your answer:**

Column 3: Is the original conclusion still supported by the evidence? (yes/no/don't know)

Column 4: Is there any other new evidence that may change this conclusion? (Author/date)

Tables are divided by Key questions. Key questions are modified for brevity; all are limited to: adults with AUDs in outpatient settings.

The findings matrix contained the first two columns of the Currency Assessment Summary Tables (Appendix D) two columns for their responses, a reference list, and the following directions:

An example of the difference in formatting between the findings matrix and the Currency Assessment is shown below. To assist reviewers, citations were formatted as (Author, Year), and the reference list (in author order) contained hyperlinks directly to the articles in PubMed. Contents of column 1 (Conclusions from the Original Systematic Review) and column 2 (New Literature Search – (Dec 2013-Jul 2017) are contained in the Currency assessment. The entire matrix is not repeated to decrease repetition in this document.

Appendix C: Materials sent to expert reviewers

Findings matrix: Example from Key Question 1

Key Question 1a: Which medications effectively reduce alcohol consumption*?

*Variably defined as: abstinence, return to any/heavy drinking; number of any/heavy drinking days, drinks per drinking day

KQ1a: Conclusions from the Original Systematic Review – Link to Report	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? (Yes/No/Unsure)	Any other new evidence? (Author/Date)
<p>Disulfiram</p> <p>No significant differences were found between disulfiram and placebo on return to any drinking (3 studies; SOE: low) and number of drinking days (2 studies; SOE: insufficient).</p> <p>No data were reported on percentage returning to heavy drinking, number of heavy drinking days, or drinks per drinking days.</p>	<p>Disulfiram</p> <p>One study reported no significant difference between disulfiram and placebo in abstaining from alcohol (n=109). (Yoshimura et al. 2014)</p> <p>A systematic review and metanalysis that included open label trials concluded that supervised disulfiram was superior to acamprosate, naltrexone and placebo. (Skinner et al. 2014)</p>		

Appendix D: Currency Assessment Summary Tables

Appendix D: Currency Assessment Summary Tables

The first column contains the original findings/conclusion from the Executive Summary, cross-walked with the Evidence Tables from Appendix D of the original Systematic Review “Pharmacotherapy for Alcohol Use Disorders”. Each row refers to a separate conclusion/finding from the full report. In the second column, we summarized results of our recent targeted literature searches. Column 3 contains expert response to “is this conclusion still supported?” When expert responses differ, they are coded as expert 1, or expert 2. Column 4 contains the AHRQ assessment of currency.

Tables are divided by Key questions (modified for brevity); all are limited to adults with AUDs in outpatient settings.

Key Question 1a: Which medications effectively reduce alcohol consumption*?

*Variably defined as: abstinence, return to any/heavy drinking; number of any/heavy drinking days, drinks per drinking day

KQ1a: Conclusions from the Original Systematic Review – Link to Report ; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
Disulfiram (Table D-2, Appendix D. Full Report) No significant differences were found between disulfiram and placebo on return to any drinking (3 studies, n=492; SOE: low) and number of drinking days (2 studies; SOE: insufficient). No data were reported on other outcomes.	Disulfiram One study reported no significant difference between disulfiram and placebo in abstaining from alcohol (n=109). ²⁹	1. May be worthwhile to update vis a vis open trials. 2. Yes (debate about how to interpret findings and ROB for older disulfiram studies is not new; the JAMA letters to the editor and our responses address that issue)	Likely current (One small study is consistent with previous conclusions)
Acamprosate (Table D-1, Appendix D, Full report) A meta-analysis of 19 studies found patients treated with acamprosate significantly decreased return to any drinking (SOE: moderate) and number of drinking days compared to placebo (SOE:	Acamprosate One study reported that acamprosate was significantly more effective over placebo in return to any drinking (n=327). ¹³	Yes	Likely current (One small study is consistent with previous conclusions)

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
moderate). No significant differences were found between acamprosate and placebo on return to heavy drinking (SOE: moderate), heavy drinking days or drinks per drinking day (SOE: insufficient for both).			
Naltrexone <i>Any dose (Table D-3, Appendix D, Full report)</i> In subjects treated with naltrexone, 4% fewer subjects returned to any drinking, 7% fewer subjects returned to heavy drinking, the treatment group had 4.6% fewer drinking days, the treatment group had 3.8% fewer heavy drinking days, and the treatment group had 0.5% fewer drinks per drinking day than the placebo group.(SOE: moderate for each) <i>50 mg oral (Table D-4, Appendix D, Full report)</i> A meta-analysis showed subjects treated with 50 mg of naltrexone were significantly less likely to return to any drinking (SOE: moderate) or heavy drinking (SOE: moderate), and had a fewer number of drinking days (SOE: moderate). <i>100 mg oral (Table D-5, Appendix D, Full report)</i> A meta-analysis showed subjects treated with 100 mg of naltrexone showed no significant difference for returning to any drinking (SOE: low) or heavy drinking (SOE: low), or having fewer of drinking days (SOE: low). <i>Injection (Table D-6, Appendix D, Full report)</i> A meta-analysis showed subjects treated with an injection of naltrexone showed significantly fewer drinking days. Subjects treated with an injection of naltrexone showed no significant difference in returning to any drinking (SOE: low) or heavy	Naltrexone One study ²⁴ using 25-50 mg Naltrexone showed no significant difference between naltrexone and placebo on return to heavy drinking or the percentage of drinking days. However, compared to placebo, naltrexone significantly decreased the number of drinks per drinking day (n=128).	Yes	Likely current; (A single small trial of a lower dose is unlikely to change prior conclusions that were based on >10 trials with >2000 participants).

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report ; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
drinking (SOE: low).			
Off-Label Therapies			
Baclofen (Table D-13, Appendix D, Full report) There were conflicting findings for return to any drinking—1 study suggested only 29% of baclofen users returned to any drinking, and another suggests 90% of baclofen users returned to any drinking. There were no significant differences in baclofen vs placebo for heavy drinking (1 study), drinking days (1 study), and heavy drinking days (1 study). No studies were identified other outcomes. SOE: insufficient for all outcomes.	Baclofen One study ²³ reported a significantly higher percentage of alcohol-abstinent days with baclofen compared to placebo (n=56). Another study ²⁶ (n=64) reported no significant difference in consumption (percentage of alcohol-abstinent days or heavy drinking days) between baclofen and placebo groups. The ALDAPIR study (n=320) showed no difference between baclofen (180 mg) and placebo in percent reaching abstinence or alcohol consumption. However, there was a trend towards reduced daily consumption on baclofen. (p=.09). ⁴³ Cochrane published a protocol for a new systematic review of the effectiveness of baclofen for AUD. ⁵² (Included for background).	1. Should be updated. 2. Unsure. This is the main drug that I've been hearing a lot more about for treating AUD (as far as one with potential to be really beneficial and used more). Synthesis of all the baclofen trials (old and new) might change conclusions for baclofen, and would be a useful contribution for an update	May not be current. (Prior conclusions were based on 2 trials (164 participants). We identified three new RCTs with 440 participants, but results are conflicting. A Cochrane review is planned.)
Buspirone (Table D-14, Appendix D, Full report) Anxious alcoholics have a significantly fewer number of drinking days while using buspirone (low SOE). There were no significant differences in returning to any drinking (2 studies, insufficient), and drinks per drinking day (1 study, insufficient).	No new studies identified	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
Citalopram (Table D-15, Appendix D, Full report) Fewer people returned to any drinking on citalopram than those on placebo, $p=.1$ (1 study, $n=62$). There was no significant difference between citalopram and placebo on number of drinking days (1 study). SOE: insufficient for all outcomes.	Citalopram One study ¹⁰ ($n=265$) reported that subjects using citalopram had a greater number of heavy drinking days than those on placebo.	1.Unsure 2.Yes	May not be current (The new study greatly increases the number of patients studied, and results conflict with prior evidence.)
Quetiapine (Table D-24, Appendix D, Full report) Quetiapine worked significantly better than placebo in reducing return to drinking (1 study). No significant difference was found for drinking days (3 studies) and heavy drinking days (3 studies). SOE: insufficient for all outcomes.	No new studies identified	Yes	Likely current
Nalmefene (Table D-20, Appendix D, Full report) Two studies ($n=1234$) showed that subjects using nalmefene had, on average, one less drink per drinking day (SOE: moderate). One study reported that 23% fewer people return to any drinking on nalmefene but another showed no significant difference (SOE: insufficient). Two studies ($n=508$) showed no significant difference for number of drinking days (low SOE). One study ($n=105$) reported no difference in return to heavy drinking (SOE: insufficient). There was a significant difference for those using nalmefene on number of heavy drinking days (1 study, $n=403$, SOE: insufficient).	One study ²⁸ reported no difference in heavy drinking days at 6 months. However, at 13 months, nalmefene significantly reduced the number of heavy drinking days over placebo (total $n=422$).	1.Yes 2. Estimates of effect and conclusions might change slightly	Likely current

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report : (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
Sertraline (Table D-25, Appendix D, Full report) The placebo group had significantly fewer heavy drinking days than the sertraline group (2 studies). (Low SOE, favors placebo). No significant differences were found and heavy drinking, number of drinking days, and drinks per drinking day (2 studies, low SOE for each outcome). SOE was insufficient for return to any drinking (1 study).	No new studies identified	Yes	Likely current
Topiramate (Table D-26, Appendix D, Full report) Subjects using topiramate had fewer drinking days fewer heavy drinking days, and fewer drinks per drinking day (3 studies, moderate SOE for each). Topiramate users had a greater percentage returning to any drinking than placebo (1 study, n=102, SOE: insufficient).	Topiramate was shown to significantly reduce drinks per drinking day and percentage of drinking days compared to placebo ¹⁵ (1 study; n=85). Another study used 100-300 mg topiramate daily after residential treatment, ²⁰ and found no significant difference in percentage of days of heavy drinking or return to heavy drinking. (n=106) One meta-analysis (7 RCTs; n=1,125) showed small to moderate effects favoring topiramate on abstinence from alcohol (the alternate measure of return to any drinking) and amount of heavy drinking. ⁸ This metaanalysis included all 4 trials from the prior SR, and all of the trials we found.	1.Unsure 2.Unsure. Would be worth including in an update if one is done	Likely current (Although single studies conflict and vary by which drinking outcome was measured, the metanalysis supports prior conclusions.)
Valproic Acid (Table D-27, Appendix D, Full report) Fewer users of valproic acid returned to heavy drinking (1 meta-analysis), had fewer drinking days (1 study), and had fewer drinks per drinking day (1 study) than the placebo group (low SOE for each). One study reported no significant difference in returning to any drinking and number of drinking days (1 study).(SOE: insufficient)	No new studies identified	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

KQ1a: Conclusions from the Original Systematic Review – Link to Report ; (See Appendix D, Strength of Evidence Tables)	KQ1a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ assessment (comment)
Insufficient evidence was found for aripiprazole, atomoxetine, desipramine, fluvoxamine, imipramine, olanzapine, ondansetron, paroxetine, and varenicline (1 study each) and for fluoxetine (2 studies),	<i>Varenicline</i> One study ¹¹ found no significant difference between varenicline and placebo on the number of heavy drinking days (n=160). Another study ²⁵ (n=40) showed that varenicline had no significant effect on number of drinking days or heavy drinking days over placebo.	1. New evidence for varenicline should be noted 2. Unsure	Likely current (Small studies found no effect.)
Off-Label medications not reported in Original Review			
	<i>Zonisamide</i> One study ¹⁵ (n=85) reported a significant reduction in drinks per day, percent of drinking days, and percent of heavy drinking days in the zonisamide group compared to placebo. <i>Levetiracetam</i> One study reported subjects in the levetiracetam group had a significant decrease in the percentage of days of heavy drinking compared to placebo(n=85). ¹⁵ <i>Gabapentin</i> There was a significant increase in the rates of abstinence and decrease in the incidence of heavy drinking for those in the gabapentin group when compared to placebo ²¹ (1 study; n=150). <i>Mecamylamine</i> RCT (n=12) found no difference in drinking outcomes between mecamylamine 10 mg and placebo. ⁴¹	1. New evidence for gabapentin should be noted. 2. Unsure	Not in scope of original SR. Included for information only.

Abbreviations: RCT=Randomized Controlled Trial; SOE=Strength of Evidence

Appendix D: Currency Assessment Summary Tables

Key Question 1b: How do medications for *compare* for reducing alcohol consumption?

KQ 1b Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ1b New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ assessment
Acamprosate vs Naltrexone (Table D-8, Appendix D, Full Report) No significant difference between acamprosate and naltrexone on return to any drinking (3 studies, n=800, SOE: moderate), return to heavy drinking (4 studies, n=1141, SOE: moderate), and number of drinking days (2 studies: SOE: low). There was insufficient data to provide analysis on acamprosate vs naltrexone on number of heavy drinking days and drinks per drinking day.	One study (n=243) compared disulfiram vs acamprosate vs naltrexone. There was no significant difference between acamprosate and naltrexone on number of drinking days, or return to any drinking. ¹⁸	Yes	Likely current
Acamprosate vs Disulfiram No studies identified. SOE: Insufficient	Acamprosate vs Disulfiram One study (n=243) compared disulfiram vs acamprosate vs naltrexone. Treatment with disulfiram was more effective than acamprosate in reducing heavy drinking and average weekly alcohol consumption, and in increasing time to the first drink, as well as the number of abstinent days. ¹⁸	1.No 2.Unsure, possible this could change conclusions for comparison vs. disulfiram	May not be current (New evidence, but single trial unlikely to change SOE.)
Disulfiram vs Naltrexone (Table D-9, Appendix D, Full Report) No significant difference between disulfiram and naltrexone on return to any drinking, number of drinking days, and number of heavy drinking days. (2 studies, high risk of bias).SOE: insufficient	Disulfiram vs Naltrexone One study (n=243) compared disulfiram vs acamprosate vs naltrexone. Treatment with disulfiram was more effective than naltrexone in reducing heavy drinking and average weekly alcohol consumption, and in increasing time to the first drink, as well as the number of abstinent days. ¹⁸	1.No 2.Unsure, possible this could change conclusions for comparison vs. disulfiram	May not be current (New evidence, but single trial unlikely to change SOE.)
Off Label Therapies Aripiprazole vs Naltrexone (Table D-29, Appendix D, Full Report) No significant difference for the number of subjects who remained abstinent, number of subjects who relapsed, mean number of abstinent days, and number of heavy drinking days between subjects	Off Label Therapies <i>Topiramate vs. Zonisamide vs. Levetiracetam vs placebo</i> One study (n=85) reported no differences by treatment group on drinking outcomes. ¹⁵	1.Yes 2.Unsure	Likely current

Appendix D: Currency Assessment Summary Tables

KQ 1b Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ1b New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ assessment
<p>using either aripiprazole or naltrexone. (1 study, n=57). SOE: insufficient.</p> <p>Sertraline vs Naltrexone (Table D-31, Appendix D, Full Report) No significant difference on outcomes between sertraline and naltrexone (1 study, n=89). SOE: insufficient.</p> <p>Topiramate vs Naltrexone (Table D-32, Appendix D, Full Report) No significant difference between topiramate and naltrexone on outcomes of interest (1 study, n=155) SOE: insufficient.</p> <p>Despiramine vs Paroxetine (Table D-30, Appendix D, Full Report) In subjects with comorbid PTSD and alcohol dependence, despiramine showed significantly fewer heavy drinking days and drinks per drinking day (1 study, n=88) SOE: insufficient.</p>			

Abbreviations: CBT=Cognitive Behavioral Therapy; QoL=Quality of Life; PTSD=Posttraumatic Stress Disorder; SOE=Strength of Evidence

Appendix D: Currency Assessment Summary Tables

Key Question 2a: Which medications improve *health outcomes* ?

KQ2a: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ2a: New Literature Search – (Dec 2013-July 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
Disulfiram (D-2) No studies reported these outcomes.	Disulfiram No studies vs. placebo were identified.	Yes	Likely current
Acamprosate (D-1) Evidence for the following outcomes are insufficient: accidents/injuries, quality of life, and mortality.	Acamprosate No studies vs. placebo were identified.	Yes	Likely current
Naltrexone (any dose) (D-3) Evidence for the following outcomes are insufficient: accidents or injuries, quality of life or function, and mortality.	Naltrexone No studies vs. placebo were identified.	Yes	Likely current
Off Label Therapies			
<i>Baclofen</i> Not reported	The baclofen group showed an increase in quality of life measures over the placebo group in one study. ²⁶ (n=64)	1.No 2.Unsure	May not be current
<i>Nalmefene (D-20)</i> On mortality, there was no significant difference between nalmefene and placebo (1 study). SOE: insufficient.	No studies were identified.	Yes	Likely current
<i>Quetiapine (D-24)</i> On mortality and quality of life, there was no significant difference between quetiapine and placebo. (1 study). SOE: insufficient.	No studies were identified.	Yes	Likely current
<i>Sertraline (D-25)</i> On quality of life, sertraline users improved scores over time. On mortality, there was no significant difference between sertraline and placebo. 1 study each. SOE: insufficient.	No studies were identified.	Yes	Likely current
<i>Topiramate D-26</i> Fewer topiramate users experienced accidents or injuries (4%) compared to placebo (11.7%, p=.01); but mortality did not differ(1 study). SOE: insufficient.	One study ²⁰ (n=106) found no significant difference in health-related quality of life between topiramate and placebo.	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

Key Question 2b: How do medications compare for improving health outcomes ?

KQ2b: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ2b: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert response	AHRQ Assessment
Acamprosate vs Naltrexone (D-8) There was insufficient evidence for quality of life (1 study). No studies reported accidents or injuries, and mortality.	Acamprosate vs Naltrexone No studies were identified.	Yes	Likely current
Acamprosate vs Disulfiram; Disulfiram vs Naltrexone No studies identified	Disulfiram vs Acamprosate vs Naltrexone One study (n=243) compared disulfiram vs acamprosate vs naltrexone. ¹⁸ In the QoL test EQ-5D, patients in all groups showed significant positive changes in sleeping, action, pain, and mood dimensions (no differences between medications). Depression decreased but did not differ between medications. Smoking decreased more in the disulfiram group than naltrexone or acamprosate groups.	1.No 2.Unsure	Likely current
Off Label Therapies			
<i>Sertraline vs Naltrexone D-31</i> One study reported no deaths in either group. <i>Topiramate vs Naltrexone D-32</i> On quality of life, there was no significant difference in WHO/PAS domains between topiramate and naltrexone, with the exception of the disability score on the employment domain, where topiramate users had lower scores. Additionally, there was a significant improvement in quality of life in topiramate users at 3 months, but not 6 months. (2 studies, high risk of bias. SOE: Insufficient)	No studies were identified.	Yes	Likely current

Abbreviations: CBT=Cognitive Behavioral Therapy; QoL=Quality of Life; SOE=Strength of Evidence

Appendix D: Currency Assessment Summary Tables

Question 3a: What adverse effects are associated with medications?

KQ 3a: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ3a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
Disulfiram (no table listed) Of the three studies that reported harms, none found statistically significant adverse events while using disulfiram. SOE: not reported	Disulfiram A 2014 study ²⁷ (n=29) reported 23 adverse events attributed to disulfiram. Three severe AEs include persistent nausea and vomiting, psychosis, and admission to inpatient treatment due to worsening physical condition.	1.Yes 2.Maybe	Likely current
Acamprosate D-33 Statistically significant harms while using acamprosate included: diarrhea (SOE: moderate, 14 studies), and nausea or vomiting (SOE: moderate, 5 studies each), withdrawal due to AE (SOE: low, 13 studies). There was low SOE for increased dizziness, headaches, and insomnia also.	Acamprosate No studies were identified.	Yes	Likely current
Naltrexone D-34 Statistically significant harms while using naltrexone included: withdrawal due to AEs (SOE: moderate, 20 studies), dizziness (SOE: moderate 17 studies), nausea (SOE: moderate 31 studies), and vomiting (SOE: moderate 11 studies). SOE was low for increased anxiety, headaches, rash, blurred vision and insomnia also.	Naltrexone One study ²⁴ (n=128) reported no serious adverse events, but an increase in sleepiness in the naltrexone group.	1.Yes 2.Maybe	Likely current
Off-Label Therapies			
Baclofen Harms were not reported.	Baclofen There were no serious adverse events related to baclofen in two studies: one RCT (n=56), ²³ and a study of comorbid alcoholism and anxiety (n=42). ²² Two non- RCTs were included for harms: Both were French studies from a national poison registry that reported high rates of baclofen poisoning after national increases in baclofen prescribing. In the larger study, there were 294 episodes of baclofen	1.No 2.Unsure, probably yes	May not be current (New RCTs report harms for over 500 subjects. Two large observational

Appendix D: Currency Assessment Summary Tables

KQ 3a: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ3a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
	<p>poisoning (overdose) in alcohol dependent persons reported over 6 years. Of these, 220 were suicide attempts and 74 were accidental overdoses. Outcomes were “severe” in 132, and 9 victims died.^{35,71}</p> <p>The ALDAPIR study reported a high frequency of at least one side effect; of which only 30-35% were moderate to severe. Serious AEs did not differ between baclofen and placebo. Common side effects (somnolence, sleep disorders, asthenia, and dizziness) were higher in baclofen than placebo groups. Of concern, anxiety increased over time in baclofen patients, from 5% during titration (weeks 1-7) to 16% during taper-off (weeks 24-26).⁴³</p> <p>An RCT of baclofen in veterans with Hepatitis C (n=180) reported no SAEs and no difference in AEs between groups.³¹</p>		<p>studies may signal increase in serious harm(intentional overdose))</p>
<p><i>Nalmefene (D-36)</i></p> <p>The following adverse events were significantly increased among nalmefene users compared to placebo: withdrawal due to adverse events, dizziness, headache, insomnia, nausea, vomiting. However, nalmefene users had lower incidence of diarrhea compared to placebo. (SOE: moderate for each)</p>	<p><i>Nalmefene</i></p> <p>One study²⁸ (n=422). Patients on nalfemene were more likely to withdraw from the study for an adverse event than placebo subjects (11 vs. 3%). SAEs were reported for 5.4% of placebo group and 6.9% of nalmefene group. Most common symptoms (>10% of nalmefene subjects were nausea, insomnia, diszziness, headache, and vomiting. The majority of serious adverse events in the placebo group (88%) and the nalmefene group (76%) were considered not related to the study medication. The exception was alcohol withdrawal syndrome, which was more common in nalmefene than placebo groups.</p>	<p>1.Yes 2.Probably not</p>	<p>Likely current</p> <p>(New evidence supports prior conclusions)</p>

Appendix D: Currency Assessment Summary Tables

KQ 3a: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ3a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
<p><i>Topiramate D-37</i></p> <p>The following adverse events were significantly increased in topiramate users compared to placebo: paresthesia and cognitive dysfunction (SOE: moderate), withdrawal due to AE and dizziness (SOE: Low)</p>	<p><i>Topiramate</i></p> <p>In subjects with alcoholism and PTSD,⁷ (n=30), one serious adverse event was impaired learning and memory.</p> <p>One study (n=85) assessed harms of Topiramate, levetiracetam and zonesamide using neuropsychological testing (i.e, Weschler Intelligence and Memory tests, WCST, Stroop, Trail-making, Rey Audio Visual and COWAT scores) as well as the A-B Neurotoxicity scale.¹⁵ They reported mental slowing, a reduction in verbal fluency and working memory as adverse events among topiramate users.</p>	<p>Yes</p>	<p>Likely current</p>
<p><i>Quetiapine</i></p> <p>No studies reported harms.</p>	<p>In one study⁹ (n=90), of subjects with bipolar disorder, the only adverse event reported was weight gain.</p>		<p>Likely current</p>
<p>Other medications not reported in the original SR</p>	<p><i>Zonisamide</i></p> <p>One study¹⁵ (n=85) reported that the only adverse events were reductions in verbal fluency and working memory.</p> <p><i>Levetiracetam</i></p> <p>One study, reported no adverse effects and no cognitive/neuropsychological impairment.¹⁵ (n=85)</p> <p><i>Gabapentin</i></p> <p>One study (n=150) stated that patients using gabapentin reported no significant adverse events²¹</p> <p><i>Mecamylamine</i></p> <p>In a small RCT (n=12) five SAEs were reported, none related to study medications.⁴¹</p>	<p>(not in original report)</p>	<p>Not in scope of the original SR. Included for information.</p>

Appendix D: Currency Assessment Summary Tables

KQ 3a: Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ3a: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
	<p><i>ABT-436</i></p> <p>A phase II trial (n=150) of ABT-436 reported that AEs (diarrhea, anxiety, and nausea) were more common in ABT-436 than placebo treated patients. Three SAEs were deemed unrelated to study medication.⁴⁴</p>		

Abbreviations: AE=Adverse Events; PTSD=Posttraumatic Stress Disorder

Appendix D: Currency Assessment Summary Tables

Key Question 3b: How do medications compare for adverse effects?

KQ3b. Conclusions from the Original Systematic Review – Link to Report (See Appendix D, Strength of Evidence Tables)	KQ3b: New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
Acamprosate vs Naltrexone D-35 The risk of diarrhea (SOE: Moderate) and insomnia (SOE: low) were higher for patients treated with acamprosate than naltrexone. The risk of headache, nausea, and vomiting were higher for patients treated with naltrexone than acamprosate (all low SOE).	Acamprosate vs Naltrexone No studies were identified.	Yes	Likely current
Acamprosate vs Disulfiram (no table) Of the two studies that compared acamprosate and naltrexone and reported harms, none found statistically significant adverse events between groups. SOE: not reported	Acamprosate vs Disulfiram No studies were identified.	Yes	Likely current
Disulfiram vs Naltrexone (no table) One study mentioned that nausea, drowsiness, abdominal pain, and diarrhea were more common among patients receiving naltrexone than those receiving disulfiram, but no statistical significance was reported. (SOE: not reported)	Disulfiram vs Naltrexone No studies were identified.	Yes	Likely current
Off Label Therapies (no table) <i>Valproic Acid vs Naltrexone</i> The valproic acid group had higher incidence of nausea than the naltrexone group. (SOE: not reported)	Off Label Therapies No studies were identified.	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

Key Question 4: Are medications effective in primary care settings?

(SOE for this KQ is not provided either in the body of the full report or Appendix D, evidence tables.)

Conclusions from the Original Systematic Review – Link to Report	New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert response	AHRQ Assessment
Disulfiram; Naltrexone No studies identified	Disulfiram; Naltrexone No studies were identified.	Yes	Likely current
Acamprosate One study found no significant effect on drinking days or heavy drinking days with use of acamprosate. No other outcomes of interest were discussed.	Acamprosate No studies were identified.	Yes	Likely current
Off-Label Therapies			
No studies identified	<i>Gabapentin</i> In primary care, there was a significant increase in the rates of abstinence from alcohol and decrease in the incidence of heavy drinking for those in the gabapentin group when compared to placebo ²¹ (1 study; n=150).	1.No 2.Unsure, this might change them a bit	Out of scope of original SR
	Included for background, neither trial describes which medications will be used: Two new studies report treatment of AUD in primary care. The Starting Treatment for Ethanol in Primary care (STEP) Trials are three parallel RCTs conducted in five Infectious Disease Clinics. ⁵⁰ The second report describes the conceptual and scientific foundation of the CHOICE model of care, results of recruitment, and baseline characteristics of the enrolled sample. ⁵¹		

Appendix D: Currency Assessment Summary Tables

Key Question 5: Does medication effectiveness vary by subgroups*?

(* men vs. women, older vs. young adults, racial or ethnic minorities, smokers, or those with co-occurring disorders)
(SOE for this KQ is not provided either in the body of the full report or Appendix D, evidence tables.)

KQ5 Conclusions from the Original Systematic Review – Link to Report	KQ5 New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
<p>Disulfiram <i>Men vs women</i> Disulfiram had a greater impact than acamprosate on reducing drinking in men (3 studies).</p> <p><i>Co-occurring disorders</i> In patients with both alcohol and cocaine dependence, disulfiram was associated with a significantly lower percentage of drinking days compared with naltrexone (1 study).</p> <p>No significant difference between disulfiram and naltrexone in veterans with an Axis 1 disorder (including depression, borderline personality disorder, antisocial personality disorder, and PTSD) on percentage of drinking days, percentage of heavy drinking days, or percentage remaining abstinent (1 study).</p>	<p>Disulfiram</p> <p><i>Co-occurring disorders</i> In comorbid alcohol and opiate addiction, disulfiram was shown to decrease alcohol use during treatment, but not drug use²⁷ (1 study; n=29).</p>	<p>1. Yes</p> <p>2. Might alter them slightly</p>	Likely current
<p>Acamprosate <i>Men vs women</i> There was no significant difference between groups on following outcomes: percentage of drinking days and heavy drinking days, and time to heavy drinking (1 study).</p> <p><i>Co-occurring disorders</i> There was no acamprosate by depression interaction or acamprosate by anxiety interaction when assessing predictors of abstinence or heavy drinking days (1 study)</p>	<p>Acamprosate</p> <p>An analysis of the COMBINE study (n=1220) showed that acamprosate was beneficial for non-obese participants with shorter abstinence (1 week or less)!. In this group, 46% of participants receiving acamprosate abstained from heavy drinking compared to 23% of those receiving placebo.⁴⁷</p>	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

KQ5 Conclusions from the Original Systematic Review – Link to Report	KQ5 New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
<p>Naltrexone <i>Men vs women</i> There was no significant difference between groups on following outcomes: percentage of drinking days and heavy drinking days, and time to heavy drinking (1 study).</p> <p>Naltrexone has a greater impact than disulfiram on reducing drinking in men (3 studies).</p> <p><i>Smokers</i> Smokers who received naltrexone had more days without drinking, and more days without heavy drinking (2 studies).</p> <p>No association between number of cigarettes smoked per day and effect of naltrexone on drinking outcomes (1 study).</p> <p><i>Co-occurring disorders</i> No naltrexone by depression interaction or naltrexone by anxiety interaction when assessing predictors of abstinence (non-drinking days) (1 study).</p> <p>There was a naltrexone by depression interaction for predictors of heavy drinking days, but no naltrexone by anxiety interaction for predicting heavy drinking days (1 study).</p> <p>No significant difference between disulfiram and naltrexone in veterans with an Axis 1 disorder (including depression, borderline personality disorder, antisocial personality disorder, and PTSD) on percentage of drinking days, percentage of</p>	<p>Naltrexone <i>Men vs women</i> A systematic review of naltrexone in women (7 studies, n=903) suggested that naltrexone may lead to modest decreases in quantity of drinks and time to relapse in women.³⁷</p> <p><i>Smokers</i> An RCT of heavy-drinking smokers given a nicotine patch and 6 weeks of counseling (n=150) showed naltrexone was not superior to placebo to reduce drinking (heavy drinking days or average drinks per week)³²</p> <p>One RCT evaluated naltrexone, OPRM genes and <u>smoking status</u>. (n=152) Naltrexone (50 mg) reduced heavy drinking at 16 weeks, but this was largely driven by improvements among smokers. When stratified, the effect of naltrexone was greater than placebo only among smokers⁴⁶</p> <p><i>Other subgroups:</i> In <u>young adults (age 18-25 years)</u>, naltrexone users showed no significant difference in percentage of heavy drinking days, and percentage of users remaining abstinent from alcohol. There was a significant decrease in the number of drinks per drinking days with naltrexone compared to placebo (n=128).²⁴</p> <p>In HIV-clinics, XR-NTX (extended release naltrexone) was feasible and well-tolerated <u>by HIV-infected individuals with AUD</u>. Retention appeared higher with XR-NTX than usual care.⁴⁰</p>	<p>1.No 2.Yes for men vs. women; for smokers, the new studies might alter conclusions some</p>	<p>May not be current</p>

Appendix D: Currency Assessment Summary Tables

KQ5 Conclusions from the Original Systematic Review – Link to Report	KQ5 New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
<p>heavy drinking days, or percentage remaining abstinent (1 study).</p> <p>With comorbid depression, patients treated with naltrexone reported longer time to relapse, but slightly lower rates of abstinence during treatment than patients treated with sertraline (1 study).</p> <p>In patients with comorbid distress/depression/anxiety and Symptom Checklist-90 scores above the median, naltrexone was associated with a longer time to lapse than acamprosate. Similar differences between naltrexone and acamprosate were found for the above-median scores for somatic distress, depression, and anxiety, though none reached statistical significance. Results for time to relapse were similar, and were not statistically significantly different (1 study).</p>	<p>For <u>HIV-infected prisoners</u>, XR-NTX at prison discharge prolonged the time to first heavy drinking day, but only for a subgroup of <u>men age 20-29</u>. Post hoc-analyses showed that those who received ≥ 4 monthly XR=NTX doses had decreased composite consumption scores.⁴⁵</p> <p>A pilot study of oral naltrexone vs. placebo for <u>HIV-infected women</u> (n=17) demonstrated feasibility, and reduced alcohol consumption in both groups. Recruitment challenges were noted. (<50% enrollment, ~ 80% retention at 7 months)³⁸</p>		
Off-Label Therapies			
<p><u>Topiramate</u> <u>Men vs Women</u> Topiramate had a greater impact than acamprosate or naltrexone on reducing drinking in men (1 study).</p> <p><u>Smoking</u> No association between number of cigarettes smoked per day and effect of topiramate on drinking outcomes (one study).</p>	<p>In subjects with PTSD, one study⁷ of topiramate showed a reduction of frequency of alcohol use, drinking amount, and symptoms of PTSD (n=30). A serious adverse event was impaired learning and memory</p> <p>In co-morbid alcohol and <u>cocaine dependency</u>, topiramate was shown to be no better than placebo in decreasing alcohol or cocaine use¹⁴ (1 study; n=170).</p> <p>An RCT of male <u>smokers</u> (n=129) showed that relapse to drinking was similar between topiramate and placebo treated groups (roughly 30%).³⁴</p>	<p>1.No</p> <p>2. These new studies might alter some conclusions as there appears to be more/new evidence</p>	Likely current
<u>Fluoxetine</u>	No new studies identified	Yes	Likely current

Appendix D: Currency Assessment Summary Tables

KQ5 Conclusions from the Original Systematic Review – Link to Report	KQ5 New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
In patients with <u>comorbid MDD</u> and alcoholism, patients using fluoxetine had fewer heavy drinking days. There were no significant differences between fluoxetine and placebo on percentage who return to any drinking (2 studies), number of drinking days (2 studies), and drinks per drinking day (2 studies). No data was reported for percentage of users who return to heavy drinking.			
Not mentioned in original SR: <i>Baclofen</i> <i>Citalopram</i> <i>Quetiapine</i> <i>Varenicline</i>	<p><i>Baclofen</i> In comorbid alcoholism and <u>anxiety</u>, one study of baclofen²² (n=42) reported a significant reduction in heavy drinking days and drinks per drinking day. In the anxiety group, but not the non-anxious group, there was a significant difference in the percentage who returned to any drinking and return to heavy drinking.</p> <p>In a pilot study of <u>heavy smokers</u>, baclofen increased the percentage of days abstaining from alcohol-tobacco co-use compared to placebo.¹⁹ (n=30) (NOTE: abstract differs from results, Figure 1, and discussion)</p> <p>An RCT of veterans with <u>Hepatitis C</u> (n=180) showed no difference in baclofen (30mg) over placebo for abstinence, heavy drinking or biomarkers.³¹</p> <p><i>Citalopram</i> One study¹⁰ (n=265) reported no significant difference between <u>depressed</u> and non-depressed patients, but a personality disorder diagnosis was associated with poor treatment responses.</p>	1.No 2. Again with baclofen, there is more evidence since the last report was written than there was available in the prior report	May not be current

Appendix D: Currency Assessment Summary Tables

KQ5 Conclusions from the Original Systematic Review – Link to Report	KQ5 New Literature Search – (Dec 2013-Jan 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
	<p><i>Quetiapine</i> Among persons with <u>bipolar disorder</u>, one study⁹ (n=90) found no significant difference for overall reduction in alcohol use between quetiapine and placebo.</p> <p><i>Doxazosin</i> (The parent study was not included; only 10 week duration). Heavy drinkers (n=41) with a <u>standing dBP >=80 mmHg</u> showed reduced drinks per week and heavy drinking days compared to placebo.³⁹</p> <p><i>Varenicline</i> In a subgroup analysis of an RCT (n=200), subjects on varenicline who decreased the number of cigarettes they <u>smoked</u> per day had a significant reduction in alcohol consumption. Varenicline also reduced consumption more than placebo for those who were <u>older (age >45)</u>, had <u>longer drinking history (>28 years)</u>, and for those whose <u>goal was reduction</u> (not abstinence).¹²</p> <p>A subgroup analysis²⁵ (n=17) suggests that <u>smokers</u> on varenicline reported significantly fewer heavy drinking days than smokers on placebo.</p>		

Abbreviations: CBT=Cognitive Behavioral Therapy; PTSD=Posttraumatic Stress Disorder

Appendix D: Currency Assessment Summary Tables

Key Question 6: Does medication effectiveness vary by genotypes?

(e.g., related to polymorphisms of the mu-opioid receptor gene [OPRM1])

(SOE for this KQ is not provided in Appendix D, evidence tables. In the body of the full report (p. 86) the authors state: “For most polymorphism-medication pairs, we found just 1 eligible study, and we graded the SOE as insufficient.”)

KQ6 Conclusions from the Original Systematic Review – Link to Report	KQ6 New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
Disulfiram 1 study identified. SOE: Insufficient.	Disulfiram In one study, there were no significant interactions between disulfiram, naltrexone, and OPRM1 (n=107 males). DBH (dopamine beta-hydroxylase) interacted with naltrexone on the primary outcome of abstinence from heavy. "T" allele carriers on naltrexone had more abstinence compared to "CC" subjects on naltrexone. "T" allele carriers on naltrexone had the highest overall rates of abstinence from heavy drinking (>90%). Also, DBH genotype interacted with disulfiram on drinks per drinking day with less drinking for subjects with the "CC" genotype than for T allele carriers on disulfiram. ⁶ In a Japanese study, patients with inactive aldehyde dehydrogenase-2 (ALDH2, n=15) significantly sustained abstinence with the use of disulfiram over placebo (100% vs. 40%, p = 0.044). ²⁹	1.No 2. Unsure	May not be current
Acamprosate 1 study identified. SOE: Insufficient.	Acamprosate Among acamprosate users (n=225), the genetic markers GRIN2B rs2058878 (P=0.0675), the minor A allele, and rs2300272 were associated with longer abstinence (P=0.049). ⁴⁸	Yes	May not be current
Naltrexone No significant difference between A-allele homozygotes and those with at least one G-allele on return to any drinking or return to heavy drinking	Naltrexone One RCT evaluated naltrexone, OPRM genes and smoking status. (n=152) Naltrexone (50 mg) reduced heavy drinking at 16 weeks, but this was	1.Needs updating 2.Probably yes	May not be current

Appendix D: Currency Assessment Summary Tables

KQ6 Conclusions from the Original Systematic Review – Link to Report	KQ6 New Literature Search – (Dec 2013-Jul 2017)	Conclusion still supported? Expert Response	AHRQ Assessment
(3 studies). SOE: not reported	largely driven by improvements among smokers. When stratified, the effect of naltrexone was greater than placebo only among smokers. Effect was not moderated by G-allele status, except that G-allele carriers had accelerated return to drinking after treatment. ⁴⁶		
Off-Label Therapies			
Topiramate, olanzapine, sertraline: 1 study each. SOE: Insufficient.	<p><i>Topiramate</i></p> <p>In a European American subsample (n=122) of one study, topiramate's effect on heavy drinking days was significantly greater than placebo only in rs2832407 C-allele homozygotes.¹⁶</p> <p>A follow-up study examined post-treatment effects of topiramate treatment for heavy drinking.¹⁷ In the European American subsample, the greater reduction in percent of heavy drinking days seen with topiramate treatment in rs2832407*C-allele homozygotes persisted throughout follow-up, with no significant effects in A-allele carriers.</p>	<p>1. No</p> <p>2. Probably yes</p>	May not be current

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